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Effect of Pharmacist-Led Interventions on (Non)Motor Symptoms, Medication-Related Problems, and Quality of Life in Parkinson Disease Patients: A Pilot Study

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Introduction: Patients with Parkinson disease (PD) use multiple drugs. This pill burden with consequent poor adherence may cause worsening of motor symptoms and drug-related problems. Therefore, a multifaceted pharmacist-led intervention program was designed to improve adherence, motor-functioning, and quality of life (QoL) in PD patients.

Methods: This prospective pilot study was performed in an outpatient PD clinic, where usual care was compared with stepwise introduction of 3 interventions: unit dose packaging (UDP), Parkinson KinetiGraph (PKG), and pharmacist-led medication review (MR).The study analyzed endpoints at 6 weeks (stage 1, usual care), 10 weeks (stage 2, UDP), 14 weeks (stage 3, UDP + PKG), and 26 weeks (UDP + PKG + MR) on motor symptoms, medication adherence, and QoL.

Results: Medication adherence improved significantly after the combined UDP, PKG, and MR intervention in nonadherent patients. On time significantly increased from 56% (±30) at stage 1, to 64% (±25) at stage 3, and to 68% (±27) at stage 4, which correlated with an increase of 1.4 and 2.2 hours in stage 3 and 4, respectively. Quality of life only improved significantly after MR (Parkinson's Disease Questionnaire with 8 domains, 21.0 ± 3.5 in stage 3 vs 19.5 ± 5.3 in stage 4, $P = 0.01$).

Conclusions: Our data did not support the added value of UDP alone or in combination with PKG. Only the combined intervention of UDP, PKG, and MR showed significant improvements in medication adherence, on time, and QoL. This supports the effectiveness of MR by a clinical pharmacist for PD patients in an outpatient setting. Therefore, this small scale study should be followed by larger-scale trials on this topic.

Key Words: Parkinson's Disease, Motor-functioning, medicine use, Medication adherence, Quality of Life, Unit dose packaging, Parkinson Kinetigraph, Drug utilization review, Clinical Pharmacist

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Parkinson disease (PD) is a neurodegenerative disease with both motor and nonmotor symptoms, substantially reducing quality of life (QoL). Since 1960, levodopa is the standard treatment replacing dopamine in the striatum.[1] Because of progression of the disease, many PD patients need increasing numbers of anti-Parkinson drugs per day.[2] Advanced PD patients with motor fluctuations may need medication up to even 7 times per day.[3] Nonmotor symptoms such as autonomic and executive dysfunction, pain, and depression, as well as presence of comorbidities give rise to an even higher pill burden.[4] Consequently, in PD treatment, medication is crucial.

However, PD patients often are nonadherent to their medication. Previous studies revealed nonadherence in 10% to 60% of PD patients.[5,6] Factors negatively associated with adherence in this population are (non) motor symptoms, lack of awareness of both carers and patients on the impact of nonadherence, polypharmacy, and presence of comorbidities.[5,7,8] Nonadherence of PD medication results in suboptimal control of PD symptoms and decreased QoL, ultimately leading to an increase of direct and indirect healthcare costs.[9] Therefore, interventions to improve adherence are urgently needed. Examples of such strategies are dosing aids and alarm systems. Dosing aids, like unit dose packaging, either or not supported by an alarm system, might help patients to improve their adherence.[10–13] However, solid data to support this are lacking.

Besides medication nonadherence, the inevitable combination of medications induces drug-related problems (DRPs), with a mean number of 2.9 DRP among community dwelling PD patients, resulting in a reduced QoL.[11] Medication review (MR) by pharmacists, a process of medication optimization in the context of clinical condition of the patients, has shown to be effective in reducing the number of DRPs and improving adherence in several settings and populations.[12] Therefore, clinical MRs have been mandated in several countries, including the Netherlands.[13] However, solid data on the effectiveness of MRs in PD patients are lacking. Only the effect on surrogate endpoints, like the number of recommendations, has been reported, without a clear effect on clinical outcomes or medication adherence.[14–16]

In conclusion, medication treatment in PD patients can be optimized. Therefore, we hypothesized that multifaceted pharmacist-led interventions, including adherence interventions and a clinical MR, would improve medication adherence and the number of DRPs as compared with usual care (UC), thereby improving motor symptoms and QoL.

METHODS

Study Design and Setting

This study was designed as a single-center, prospective, observational pilot study with PD patients, where UC was compared with a stepwise introduction of 3 pharmaceutical care interventions over a period of 6 months. Patients were included from September 2013 to May 2014 and served as their own controls.

Patient Selection

Consecutive PD patients were selected from the neurological outpatient clinic of the University Medical Centre Groningen, the Netherlands, a PD referral center for the Northern region, specialized in advanced therapies. Therefore, patients attending this outpatient clinic generally are in an advanced disease stage. Patients were eligible if they had PD according to the United Kingdom Brain Bank criteria,[17] had presence of motor and/or nonmotor

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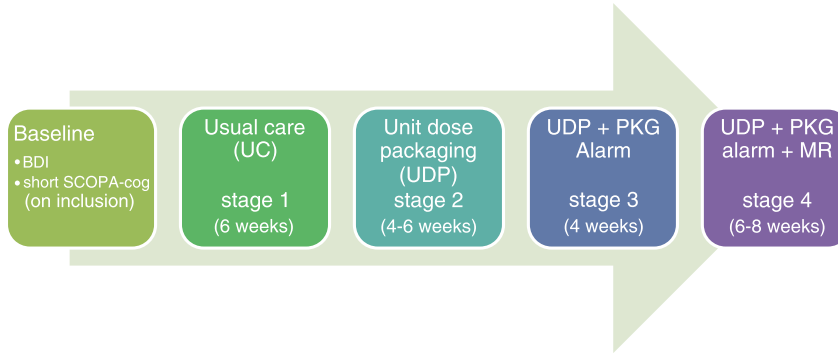

FIGURE 1. Study design and clinical endpoints. BDI, beck depression inventory; BMQ, beliefs about medicines questionnaire; MARS, medication adherence response scale; MR, medication review; NMSQ, non-motor symptom questionnaire; PDQ8, Parkinson's disease questionnaire 8 domains; PKG, Parkinson kinetic graph accelerometer; SCOPA-cog, scales for outcomes in Parkinson's disease-cognition; TRS, treatment response scale.

fluctuations, and used at least one anti-Parkinson drug (Anatomic Therapeutic Code N04). Patients had to understand the procedures and had to be able to sign informed consent.

Patients eligible for an advanced therapy like deep brain stimulation (DBS), levodopa, or apomorphine infusions introduced within 6 months after inclusion were excluded, as well as patients already on unit dose packaging systems, nursing home patients, or patients with a life expectancy of less than 6 months. Prior usage of other adherence devices was no exclusion criterion: patients could continue to use it on their own judgment.

Definition of 3 Pharmacist-Led Interventions

Interventions were introduced stepwise, with a variable implementation period of 4 to 8 weeks per intervention stage. This variable period was caused by the extra time needed for implementation of UDP during the second intervention stage (up to 6 weeks) or introduction of medication changes resulting from the MR (up to 8 weeks).

Baseline conditions consisted of UC, followed by 3 sequentially introduced interventions, consisting of UDP, Parkinson KinetiGraph (PKG) alarm, and an MR (Fig. 1). In stage 1, UC was performed by specialized PD nurses and pharmaceutical care was provided by the community pharmacist or dispensing general practitioner of the patient. Usual care by specialized PD nurses included (1) clarifying and monitoring the diagnosis of PD, (2) guidance on managing drug-intake (eg, advise about swallowing difficulties), and (3) referrals to other professionals. Usual pharmaceutical care consisted of screening electronically generated alerts on interactions, double medication, and dosing alerts. Prescribers were contacted on indication, according to the Dutch Pharmacy Standard as mandated by the Royal Dutch Pharmaceutical Society.[18]

Stage 2 consisted of the introduction of robot-dispensed unit doses. Oral solid drugs were packed in disposable bags per dosing moment and labeled with patient data, drug contents, and date/time for intake.[19]

The PKG is a watch-like device, worn on the most affected arm, which provides a vibratory alarm at the time of programed levodopa intakes. During stages 1 and 2, PKG was worn for motor registrations only and the alarm was switched off, whereas in stages 3 and 4, the vibratory alarm was provided. Patients had to acknowledge their drug intakes by pressing a button on the PKG during all 4 measurement periods. Furthermore, PKG is an accelerometry-based system with a data logger and 2 algorithms, providing a likelihood of being either dyskinetic or bradykinetic. Parkinson KinetiGraph produces a report on these motor states, based on data from 6 to 8 days, measuring from 5 AM to 10 PM per intervention stage.[20]

Finally, in stage 4, an MR was performed, including a structured interview with the patient by the clinical pharmacist, who also executed tests on mood and cognition, as important covariables in drug adherence. The pharmacist had access to the hospital patient records. Furthermore, medication and medical histories were received from the community pharmacy and GP, to perform a structured MR, according to current standard and guidelines and identify potential DRPs.[13] Drug-related problems are all problems related to the use of approved drugs. These can be divided into adverse drug reactions (including drug-drug and drug-disease interactions) and medication errors (either by the patient, the healthcare professional, or the system).[21] Focus points in PD patients are the use of anticholinergics, antihypertensives/cardiac medication, proton pump inhibitors, and vitamins B and D status although the analysis was always intending to identify all DRPs. After this assessment, the pharmacist and neurologist met to discuss the most important DRPs, which were prioritized as a basis for adjustment of the existing pharmacotherapy. During this session, motor scores from the PKG reports were used for analysis and were included in the final conclusions. Other nonneurologic DRPs were discussed with the responsible physician (GP or medical specialist). Proposed medication changes were discussed with the individual patients. The clinical pharmacist was responsible for the monitoring and follow-up of these changes.[13]

Definition of Endpoints

Depression and impaired cognition are independent risk factors for nonadherence.[22] Therefore, at baseline, all patients were screened for depression and PD-related dementia by Beck Depression Inventory (BDI) and a shortened version of the Scales for outcomes in Parkinson's disease cognition (SCOPA-cog). [23,24] Cognitive testing consisted of 4 items, each representing the most sensitive item of the 4 domains of the SCOPA-Cog battery. Demographic variables like age, gender, and disease duration and presence or absence of DBS were collected from hospital records.

During each intervention stage, all endpoints were assessed at least 2 weeks after having started the intervention. Medication adherence and influences on it were scored by respectively the Medication Adherence Response Scale (MARS), the Beliefs about Medicines Questionnaire (BMQ), and the response to PKG alarms during each intervention stage. The MARS is a 5-item questionnaire measuring medication adherence on a 5-item Likert scale. Domains include intentional and nonintentional adherence questions. The overall MARS score ranges from 5 to 25. A value of

TABLE 1. Description of DRPs

Category	DRP	Type of Intervention and Example
Indication	Additional drug therapy required	Start: Patient has a high BDI score with obvious depressive symptoms without antidepressants.
	Unnecessary drug therapy	Stop: Patient uses low dose of aspirin without a high cardiovascular risk profile.
Effectiveness	Ineffective drug therapy	Patient uses pramipexole, immediate release, once daily.
	Dosage too low	Dosage change: a patient on simvastatin 10 mg once daily
Safety	Adverse drug event	Substitution: patient with urge incontinence and mild cognitive impairment on oxybutinin
	Dosage too high	Dose change: patients on long term, high-dose proton pump inhibitors
Drug use	Drug intake problem	A patient uses 6 times a day levodopa and is unable to organise this.

For each DRP, Anatomic Therapeutic Code, type of DRP, proposed intervention, and implementation were documented.

23 or more was considered as adherent, and lower values as nonadherent.[25] The BMQ measures patient's beliefs about the necessity of prescribed medication and their concerns about potential adverse effects, both with 5 Likert questions each. By subtracting the concerns score from the necessity score, a differential score can be calculated, ranging from minus 20 to plus 20. Positive scores indicate the perceived benefit of medication outweighs the harm. The BMQ was dichotomized on the mean BMQ differential score of 4 (below or equal to 4 means a perception of having no benefit).[26] Each confirmation of levodopa intake after a PKG alarm was registered.

Motor symptoms were scored hourly on the treatment response scale (TRS) during 18 h/d. Treatment response scale scores range from −3 to +3, where −1 to +1 represented "on state" without dyskinesia (DK), −2/−3 "off state" with moderate to severe bradykinesia, and +2/+3 "on state" with moderate to severe DK.[27] The overall motor scores were expressed as percentages per day of being in a particular TRS level. Nonmotor symptoms and QoL were scored using the Non-Motor Symptom Questionnaire (NMSQ), consisting of 30 items and the Parkinson's Disease Questionnaire with 8 domains (PDQ-8), respectively. All positive responses ("yes") on the NMSQ were summed for each patient (Non-Motor Symptom score). The PDQ consists of 8 items. Each item is scored from 1 ("never") to 5 ("always"). Higher scores indicate a higher presence of nonmotor symptoms and a worse QoL.[28,29] The NMSQ was dichotomized based on the median of all patients (11) and PDQ-8 on the mean of all patients (19). Drug-related problems were classified and identified according to the structure of Strand et al.[30] Categories were indication, effectiveness, safety, and drug use. From these definitions, DRPs were derived as described in Table 1. All potential DRPs were entered in Service Apotheek Medication Review Tool and analyzed in Microsoft Excel 2010.

The study was approved by the institutional review board of the University Medical Centre Groningen.

TABLE 2. Baseline Characteristics

	Value (n = 23)
No. females (%)	9 (39)
Age, mean, y (±SD)	66.8 (8.6)
No. PD tremor-dominant patients (%)	5 (21)
No. patients with DBS (%)	6 (26)
Disease duration, mean, y (± SD)	10.3 (7.4)
BDI*score, mean (range)	11.0 (1–30)
Abnormal SCOPA-Cog† domains, median (range)	1.0 (0–4)
No. medications per patient, median (range)	8.0 (2–17)
No. PD medications per patient, median (range)	3.0 (1–5)

*BDI.

†SCOPA-Cog.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS 22. Data were primarily analyzed using descriptive statistics. Wilcoxon signed rank analysis was used to compare changes in the time being "on," "off," or dyskinetic. Possible independent contributions of the 3 interventions on the endpoints were analyzed by dichotomizing possible contributing factors.

RESULTS

In total, 37 patients were screened for eligibility and gave informed consent. Ten patients were excluded for different reasons. Three patients refused to participate because they did not want to change their drug intake habits, 4 patients had difficulties with the UDP system, 1 patient did not want to wear the PKG due to edema, 1 patient had an allergic reaction on the dispended generic medication, and 1 patient had difficulties with delivery of medication via postal service. Thus, finally, 27 patients were included, whereas 23 patients completed all interventions. Baseline characteristics are summarized in Table 2.

More than 50% of included patients had at least significant changes in 1 cognitive domain. The same was true for the presence of a (possible) depression (22% depressed [BDI, >16]; 30% possibly depressed [BDI, between 9 and 17]).

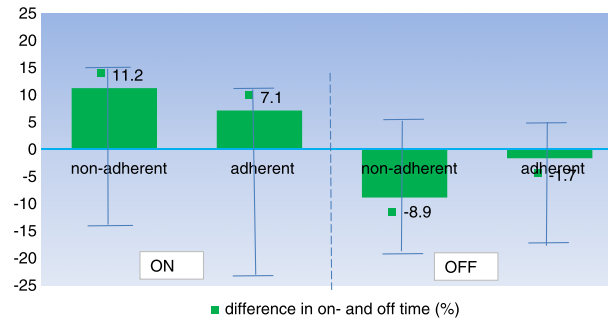

FIGURE 2. Change (stage 4 minus stage 1) in motor scores: influence of adherence on motor performance.

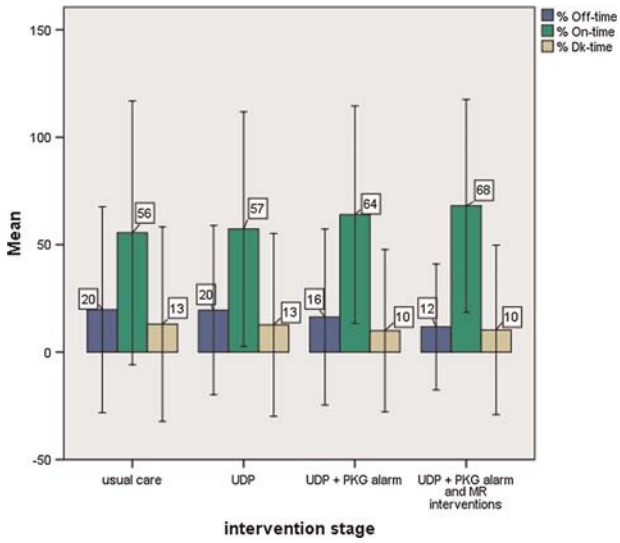

FIGURE 3. Effect on motor symptoms by TRS scores (mean change in % of time) per intervention stage (n = 23).

Effect on Medication Adherence

Neither MARS nor BMQ showed a significant change after any of the interventions. However, if nonadherent patients were selected (MARS score, <23 at baseline; n = 11), a significant improvement in on time was seen after the combination of all 3 interventions (47.9% [±29.6] vs 59.1% [±27.8], $P = 0.049$). This positive change of 11.2% was not seen after UDP alone, or in combination with the PKG alarm, but only after the addition of MR (Fig. 2). No significant effects on "off time" and DK were seen in the noncompliant group.

A positive perception of medication benefit as measured by the BMQ (4 or higher) resulted in a significant improvement in the percentage on time after introduction of all 3 interventions, as compared with UC: 55.3% (±32.3) versus 68.6% (±29.4) $P = 0.035$. This improvement corresponds with 2.3 hours extra on time.

The PKG alarm was activated in 58.2% (n = 1253) of all drug intakes (n = 2167). Only 66% of these were registered on time (<15 minutes after drug- intake).

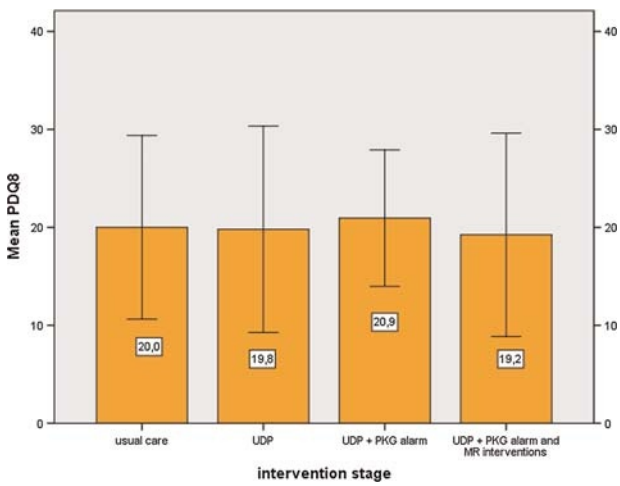

FIGURE 4. Mean PDQ-8 scores per intervention stage (n = 23).

Effect on Motor Symptoms

The mean on time per day as scored by the TRS (−1 to +1) changed from 54% (±30) during UC (stage 1) to 64% (±25) after UDP + PKG alarm (stage 3) and 68% (±27) after UDP + PKG alarm and MR (stage 4), both significant changes versus UC (Fig. 3). This equals an increase in on time of 1.8 and 2.5 hours, respectively. The percentage off time and DK did not show significant changes (12% and 10% in stage 4). The addition of the alarm contributed especially to the increase of on time, whereas MR had an additional positive impact on top of the PKG alarm. Unit dose packaging showed no significant changes in "on time."

Depressed patients had a significant improvement in on time on the TRS (−1 to +1), changing from 30% (±31) in stage 1 to 53% (±30) after UDP + PKG alarm and 49% (±36) after UDP + PKG alarm + MR, which were both significantly different from UC. The results for nondepressed patients were not significantly different from UC: 67% (±26) versus 73% (±20) after UDP + PKG alarm and 76% (±18) after UDP + PKG alarm + MR.

Patients with impaired cognition also showed a significant change in on time from 48% (±31) during UC, to 62% (±26) after UDP + PKG alarm and 55% (±32) after UDP + PKG alarm + MR. No significant differences were found in cognitively intact patients: from 58% (±30) to 67% (±25) (UDP + PKG alarm) and 69% (±23) UDP + PKG alarm + MR).

Cognitive and/or depression scores at baseline were not correlated with the off time, DK scores, or QoL.

Effect on QoL

The PDQ-8 scores are shown in Figure 4. Only the combination of UDP + PKG alarm + MR showed a small but significant change in the PDQ-8 as compared with UDP + PKG alarm (20.9 ± 3.5 vs 19.2 ± 5.3, $P = 0.01$).

Effect on Nonmotor Symptoms

No significant effects were seen on nonmotor symptoms after any of the applied interventions, including the combination of all interventions.

TABLE 3. Intervention Types

	No. DRPs (%)
Medication change	80 (48)
– Dopaminergic medication	32 (38)
– Cardiac medication	19 (24)
– Vitamins	9 (14)
– Other medications*	20 (20)
Type of medication change	
– Start of drug	18 (23)
– Dosage change	16 (20)
– Discontinuation	14 (17)
– Substitution	32 (40)
Other interventions	
– Monitoring	32 (19)
– Information/advice	32 (19)
– Other	21 (14)
Total no. interventions	165 (100)

*Laxatives, pain medications, spasmolytics, proton pump inhibitors, domperidone.

Drug-Related Outcomes

Overall, 165 DRPs were registered and discussed with the patient, which means an average of 4.6 (±1.3) DRPs per patient. In total, 86% (n = 142) of these DRPs lead to a change, in medication in 48% (n = 80), from which 38% (n = 32) was related to dopaminergic (levodopa, dopamine agonists) medication. The majority of the nondopamineric medication interventions was related to cardiac (β-blockers, ace inhibitors, diuretics) medication (24%, n = 19) and vitamin preparations (14%, n = 9). Most important types of medication changes were related to newly introduced medication (23%, n = 18), dosage change (20%, n = 16), and discontinuation of medication (17%, n = 14) (Table 3). Ten percent of rejected suggestions were due to patient unwillingness to change medication and 4% to the responsible physician.

DISCUSSION

To our knowledge, this is the first pharmacist-led multifaceted intervention study resulting in a significant improvement of clinical outcomes in PD patients. The results are remarkable, because most patients were in an advanced stage of PD, which makes it very difficult to realize a clinical significant improvement. Furthermore, more than 50% of included patients, who are generally excluded from trials, had at least mild cognitive impairment. Overall, patients showed a significant improvement of 12% (2.2 hours) in their on time and a nonsignificant decline of 10% (1.8 hours) in off- time after introduction of pharmacist-led interventions including UDP, PKG alarms, and MRs.

Because each intervention was on top of previously started interventions and examined in combination, it is not easy to draw firm conclusions on the effects of the separate interventions. Only the effects of UDP could be analyzed separately. Many patients receive automatically UDP support from their pharmacists. However, our study could not find positive effects of UDP in this population, not even in the cognitively impaired or depressed subgroup. We have to be cautious in drawing firm conclusions though, owing to the small sample size and the lack of a control group.

In the self-judged nonadherent group, the best improvement of motor symptoms resulted from the addition of MR. These findings suggest that specific interventions should be selected based on patient profiles and analyzed by F.I., a clinical pharmacist, as was the case in our study.

Previous publications on pharmacist activities in an outpatient neurology clinic on the number of interventions, and patient and healthcare satisfaction were less positive as compared with our data.[15] In total, 69 drug therapy recommendations in 131 patients were executed, whereas 21% possibly resulted in an improved outcome. The much higher number of accepted recommendations in our study is caused very likely by the colocation of the clinical pharmacist, working in close collaboration with other healthcare professionals in our PD outpatient clinic. A recent meta-analysis on colocated pharmacists in a general surgery practice confirmed that positive effects were seen more often in studies involving a pharmacist, delivering multifaceted interventions in close collaboration.[31] Another study among Maltese pharmacists and PD patients showed significant improvements of adherence and QoL, whereas a recently published randomized clinical trial, using 5 intensive home visits of 40 minutes during 3 months by a clinician, also reported positive outcomes on adherence and QoL.[29,32] Unfortunately, our study did not show an overall effect on adherence or BMQ scores over time, except from the improvement of motor symptoms in our nonadherent patients in stage 4 of this trial. Finally, the PKG alarm was used adequately in only 40% of drug intakes, which, like the MARS, does not support its role in drug adherence, although the PKG alarm had the biggest effect on motor scores in depressed and cognitively impaired patients. This puts adherence tools in general on debate and may induce the discussion on this subject.

In conclusion, patients showing nonadherence, with a higher perception of medication benefit and probably a low QoL, have a bigger chance of improving their motor performance and/or QoL, especially in combination with MRs.

Notwithstanding the aforementioned strengths, some limitations have to be discussed as well. One single pharmacist performing interventions in a single center, on a small population, fuels the debate if these data can be generalized. Furthermore, the final number of patients analyzed was small, and therefore, large confidence intervals were found. Hence, results should be interpreted with caution. One of the reasons that the final group to be analyzed was relatively small was caused by the serious drop-out rate (1/3). This is explained very likely by the case mix of our PD outpatient department, existing of advanced patients with symptom progression, and increasing difficulty with fluctuating on-off symptoms. A study period of several months therefore was beyond the scope of many of these patients.

CONCLUSIONS

Our data support the effectiveness of a clinical pharmacist at an outpatient PD clinic, to optimize clinical symptoms in selected subgroups of PD patients. The appropriate interventions should be selected based on the presence of adherence, medication benefit perception, and QoL scores, to yield the best improvement. A future prospective randomized trial with a parallel set-up of different interventions, as compared with UC, will be necessary to solve the methodological issues as mentioned before.

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